CHAPTER

60 Qualitative and Quantitative Coronary Angiography

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KEY POINTS

- Although clinical outcomes after percutaneous coronary intervention (PCI) have substantially improved over the past decade with use of coronary stents, assessment of coronary lesion complexity remains valuable in estimating early and late procedural risk. Aggregate scores that consider both the vessel patency and underlying lesion morphology provide the most predictive information for estimating outcome. Longer lesions, thrombus-containing lesions, degenerated saphenous vein grafts, severe tortuosity and angulation, and total coronary occlusions hold the highest risk for failure with PCI.
- Assessment of both myocardial blood flow and myocardial perfusion is useful in predicting prognosis in patients with ST-segment elevation myocardial infarction (STEMI) and may also be valuable in predicting events in patients with non-ST-segment elevation myocardial infarction as well. More quantitative indices are preferred over more qualitative ones in order to assess the value of new drugs and devices in patients with STEMI.
- Interventional cardiologists remain firmly wedded to the coronary angiogram for the assessment of lesion severity before and after PCI, reserving the physiologic assessment of intermediate lesions to adjunct modalities such as fractional and coronary flow reserve measurements. However, more reliable and reproducible methods of severity assessment using quantitative angiography have provided important insights into the mechanism of benefit for new drugs and devices in patients undergoing coronary intervention.
- Late clinical restenosis can be predicted by the quantitative measurement of percent diameter stenosis and late lumen loss in patients undergoing drug-eluting stent placement compared with bare metal stent placement. More studies are needed to evaluate whether these angiographic measurements correlate with relevant differences in late clinical outcome when two drug-eluting stents are compared.
- Quantitative angiographic methods remain an extremely important tool for the assessment of outcome after new device and drug therapy in patients undergoing intervention for ischemic heart disease.

Percutaneous coronary intervention (PCI) has evolved dramatically over the past 2 decades, fundamentally altering the management of ischemic cardiovascular disease. Coronary stents and, more recently, drug-eluting coronary stents (DESs), are currently used in 80% to 90% of PCI procedures. Coronary arteriography is a fundamental component of PCI, providing prognostic information about the baseline lesion morphology and severity, quantification of anterograde perfusion, and adequacy of the final angiographic result. Conventional "visual" angiography has formed the cornerstone of clinical decision-making for patients undergoing cardiovascular intervention, but insights from more quantitative analysis of procedural and late angiograms have permitted a mechanistic understanding of the relative value of new devices and drugs developed for the treatment of ischemic cardiovascular disease. Refinements in the angiographic determinants of procedural complications, thrombosis, and restenosis have permitted more appropriate device evaluation and selection for patients undergoing these procedures.

The purposes of this review are threefold. First, the standard criteria used to stratify the baseline procedural risk in patients undergoing PCI are reviewed. These criteria have been modified since the availability of DESs, and a number of new predictive scores for early and late outcome after stent placement have

been identified. Second, newer methods to assess myocardial perfusion beyond coronary flow that provide important prognostic information for patients with acute myocardial infarction (AMI) are reviewed. Third, the quantitative angiographic methods used for evaluating early and late procedural outcome after PCI are outlined, including a discussion of the value of these indices as surrogates for clinical outcome.

QUALITATIVE ANGIOGRAPHY

Assessment of procedural risk for PCI begins with accurate definition of the baseline coronary anatomy. Predictors for an adverse procedural outcome after balloon angioplasty were identified in early series, but a standardized approach to the assessment of lesion morphology in patients undergoing PCI was lacking until the late 1980s. Contemporary refinement of these criteria was necessary after the introduction of coronary stents in order to more appropriately estimate procedural risk in the new millennium of device intervention.

Update On The ACC/AHA Task Force on Lesion Morphology

A joint task force of the American College of Cardiology (ACC) and American Heart Association (AHA) established criteria in 1988 to estimate procedural success and complication rates after balloon angioplasty based on the presence or absence of specific high-risk lesion characteristics.[1] Although these criteria were developed based solely on the task force's clinical impressions (Table 60-1), their estimates of procedural success and complications were closely correlated with the procedural outcomes demonstrated in patients undergoing multivessel balloon angioplasty.[2] Lesion characteristics associated with an adverse outcome included chronic total occlusion, high-grade stenosis, stenosis on a bend of 60 degrees or more, and location in vessels with proximal tortuosity.[2] With improvements in equipment design and periprocedural anticoagulation, better outcomes were reported after balloon angioplasty, although the most complex lesion morphologies (i.e., "type C" lesions) were still associated with less satisfactory procedural outcomes.

Other composite risk scores were proposed as alternatives to the ACC/AHA score with the availablility of new coronary devices, including coronary stents.[3,4] The Society for Cardiac Angiography and Interventions (SCAI) Registry evaluated 61,926 patients (74.5% received stents) from the ACC National Cardiovascular Data Registry and classified their lesions into four groups: non-type C patent, type C patent, non-type C occluded, and type C occluded (Table 60-2).[3] These more simplified criteria provided better discrimination for success or complications than the ACC/AHA original classification with a c statistic of 0.69 for success using the ACC/AHA original classification system, 0.71 using the modified ACC/AHA system, and 0.75 for the SCAI classification.[3]

The Mayo Clinic Risk Score was constructed by adding integer scores for the presence of eight morphologic variables and was compared with the ACC/AHA risk score in 5064 patients undergoing PCI, of whom 183 (4%) experienced an adverse event (death, Q-wave myocardial infarction, stroke, emergency coronary artery bypass graft).[4] The Mayo Clinic risk score offered significantly better risk stratification than the ACC/AHA lesion classification for the development of cardiovascular complications, whereas the ACC/AHA lesion classification was a better system for determining angiographic success.[4]

Risk Assessment Using Specific Lesion Morphologic Criteria

Despite the value of risk scores in estimating aggregate procedural risk, there are several limitations of these criteria as applied to individual patients.

Table 60-1. ACC/AHA Characteristics of Type A, B, and C Coronary Lesions

Type A lesions—high success (>85%), low risk	
Discrete (<10 mm)	Little or no calcium
Concentric	Less than totally occlusive
Readily accessible	Not ostial in location
Nonangulated segment (<45 degrees)	No major side branch involvement
Smooth contour	Absence of thrombus
Type B lesions—moderate success (60%-85%), moderate risk	
Tubular (10-20 mm length)	Moderate to heavy calcification
Eccentric	Total occlusion <3 mo old
Moderate tortuosity of proximal segment	Ostial in location
Moderately angulated (45-90 degrees)	Bifurcation lesion requiring double guidewire
Irregular contour	Some thrombus present
Type C lesions—low success (<60%), high risk	
Diffuse (>20 mm length)	Total occlusion >3 mo old
Excessive tortuosity of proximal segment	Inability to protect major side branches
Extremely angulated segment (>90 degrees)	Degenerated vein grafts with friable lesions

Modified from Ryan TJ, Faxon DP, Gunnar RP, et al: Guidelines for percutaneous transluminal coronary angioplasty: A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). J Am Coll Cardiol 1988;12:529-545.

Table 60-2. SCAI Lesion Classification System: Class I-IV Lesions

Type I lesion (highest success expected; lowest risk)
(1) Does not meet ACC/AHA criteria for type C lesion
(2) Patent

Type II lesion
1. Meets any of the following ACC/AHA criteria for type C lesion:
   Diffuse (>2 cm length)
   Excessive tortuosity of proximal segment
   Extremely angulated segments >90 degrees
   Inability to protect major side branches
   Degenerated vein grafts with friable lesions
2. Patent

Type III lesion
1. Does not meet ACC/AHA criteria for type C lesion
2. Occluded

Type IV lesion
1. Meets any of the following ACC/AHA criteria for type C lesion:
   Diffuse (>2 cm length)
   Excessive tortuosity of proximal segment
   Extremely angulated segments >90 degrees
   Inability to protect major side branches
   Degenerated vein grafts with friable lesions
2. Occluded

Modified from Krone R, Shaw R, Klein L, et al: Evaluation of the American College of Cardiology/American Heart Association and the Society for Coronary Angiography and Interventions lesion classification system in the current "stent era" of coronary interventions (from the ACC-National Cardiovascular Data Registry). Am J Cardiol 2003;92:389-394.

Identification of lesion characteristics, such as eccentricity, irregularity, angulation, and tortuosity, is limited by substantial interobserver variability. Agreement with ACC/AHA classification was noted in only 58% of lesions in one series, with disagreement by two classification grades noted in almost 10% of lesions.[2] Accordingly, rather than a composite score, description of individual morphologic features may be more predictive of early and late outcome after PCI. Some ACC/AHA morphologic features are associated with a complicated procedure (e.g., thrombus, saphenous vein graft [SVG] degeneration, angulated segments), whereas others are associated with an unsuccessful but uncomplicated procedure (e.g., chronic total occlusions, diffuse disease). As an alternative to providing a composite lesion complexity score, estimation of procedural risk based on the presence of one or more specific adverse morphologic features may be more useful (Table 60-3).

Irregular Lesions

With the advent of coronary stents, the prognostic importance of irregular lesions has been diminished substantially, although identification of an irregular plaque at angiography suggests the presence of an acute coronary syndrome and intracoronary thrombus. Semiquantitative and quantitative measurements of lesion irregularity were developed in the

Table 60-3. Definitions of Preprocedural Lesion Morphology

Feature	Definition
Eccentricity	Stenosis that is noted to have one of its luminal edges in the outer one-quarter of the apparently normal lumen
Irregularity	Characterized by lesion ulceration, intimal flap, aneurysm, or "sawtooth" pattern
Ulceration	Lesion with a small crater consisting of a discrete luminal widening in the area of the stenosis is noted, provided that it does not extend beyond the normal arterial lumen
Intimal flap	A mobile, radiolucent extension of the vessel wall into the arterial lumen
Aneurysmal dilation	Segment of arterial dilation larger than the dimensions of the normal arterial segment
"Sawtooth pattern"	Multiple, sequential stenosis irregularities
Lesion length	Measured "shoulder-to-shoulder" in an unforeshortened view
Discrete	Lesion length <10 mm
Tubular	Lesion length 10-20 mm
Diffuse	Lesion length ≥20 mm
Ostial location	Origin of the lesion within 3 mm of the vessel origin
Lesion angulation	Vessel angle formed by the centerline through the lumen proximal to the stenosis and extending beyond it and a second centerline in the straight portion of the artery distal to the stenosis
Moderate	Lesion angulation ≥45 degrees
Severe	Lesion angulation ≥90 degrees
Bifurcation stenosis	Present if a medium or large branch (>1.5 mm) originates within the stenosis and if the side branch is completely surrounded by stenotic portions of the lesion to be dilated
Lesion accessibility (proximal tortuosity)	
Moderate tortuosity	Lesion is distal to two bends ≥75 degrees
Severe tortuosity	Lesion is distal to three bends ≥75 degrees
Degenerated SVG	Graft characterized by luminal irregularities or ectasia comprising >50% of the graft length
Calcification	Readily apparent densities noted within the apparent vascular wall at the site of the stenosis
Moderate	Densities noted only with cardiac motion before contrast injection
Severe	Radiopacities noted without cardiac motion before contrast injection
Total occlusion	TIMI 0 or 1 flow
Thrombus	Discrete, intraluminal filling defect is noted with defined borders and is largely separated from the adjacent wall; contrast staining may or may not be present

SVG, saphenous vein graft; TIMI, Thrombolysis in Myocardial Infarction.

early 1990s to better characterize lesion morphology in patients with acute coronary syndromes, but these methods have not found clinical utility independent of other clinical risk factors.

Angulated Lesions

Vessel curvature at the site of maximum stenosis should be measured in the most unforeshortened projection using a length of curvature that approximates the balloon length used for coronary dilation. Although balloon angioplasty of highly angulated lesions is associated with an increased risk for coronary dissection, in the era of coronary stenting the greatest impediment of angulated lesions is inability to deliver the stent to the stenosis and straighten the arterial contour after stent placement, which may predispose to late stent fracture.

Lesion Calcification

Coronary artery calcium is an important marker for coronary atherosclerosis. Conventional coronary angiography has limited sensitivity for the detection of smaller amounts of calcium and is only moderately sensitive for the detection of extensive lesion calcium (60% and 85% sensitivity for three- and four-quadrant calcium, respectively).[5] The presence of coronary calcification reduces the compliance of the vessel and may predispose to dissection at the interface between calcified plaque and normal wall after balloon angioplasty. The presence of coronary calcification also reduces the ability to cross chronic total occlusions; moreover, in severely calcified lesions, stent strut expansion is inversely correlated with the circumferential arc of calcium.[6]

Rotational atherectomy is the preferred pretreatment method in patients with severe lesion calcification, particularly ostial lesions, and it facilitates the delivery and expansion of coronary stents by creating microdissection planes within the fibrocalcific plaque. Even with these contemporary methods, however, the presence of moderate or severe coronary calcification is associated with reduced procedural success and higher complication rates,[7] including stent dislodgement. In less severely calcified lesions, no difference in restenosis rate was found after paclitaxel-eluting stent implantation in calcified versus noncalcified vessels.[8] Calcification noted within SVGs is usually within the reference vessel wall rather than within the lesion and is associated with older graft age, insulin-dependent diabetes, and history of smoking.[9]

Degenerated Saphenous Vein Grafts

SVGs develop progressive degeneration over time, with 25% occluding within the first year after coronary bypass surgery[10] and 50% developing occlusion within 10 years after surgery. Although coronary stents and, more recently, DESs[11] reduce restenosis rates compared with balloon angioplasty, only embolic protection devices have reduced procedural complications.[12,13] One exception may be in patients treated for in-stent restenosis (ISR), where embolic protection may not be required. Self-expanding stents made with expanded polytetrafluoroethylene (ePTFE) provide no additional advantage over noncovered balloon-expandable stents on the development of early complications or late restenosis.[14]

The risk for embolic complications appears to be related to both the degree of overall graft degeneration and the length of the lesion.[15] Using angiographic assessments of the extent of graft degeneration and estimated volume of plaque in the target lesion, independent correlates of increased 30-day major adverse cardiac event rates were more extensive vein graft degeneration ($P = .0001$) and bulkier lesions (larger estimated plaque volume, $P = .0005$).

Thrombus

Conventional angiography is relatively insensitive for the detection of coronary thrombus. The presence of angiographic thrombus, usually identified by the appearance of discrete, intraluminal filling defects within the arterial lumen, is also associated with a higher, albeit widely variable (6% to 73%), incidence of ischemic complications after PCI. The primary complications related to PCI of thrombus-containing lesions are distal embolization and thrombotic occlusion, with the risk for complications with angiographic thrombus relating to the size of the coronary thrombus. Routine rheolytic thrombectomy provides no benefit in patients with AMI,[16] although it may be useful for patients with a large thrombus burden. A number of aspiration catheters have been used in patients with AMI and large thrombus burden, but large-scale studies are lacking.

Ostial Location

Ostial lesions are defined as those that begin within 3 mm of the origin of the coronary artery; they are classified as aorto-ostial and nonaorto-ostial. Balloon angioplasty of ostial lesions is limited by suboptimal procedural outcome, primarily due to technical factors such as difficulties with guide catheter support, lesion inelasticity precluding maximal balloon expansion, and early vascular recoil limiting the acute angiographic result. Debulking techniques such as directional and rotational atherectomy improve the compliance of the aorto-ostial lesion but have had limited effect on preventing late restenosis.

Coronary stenting, more recently with DESs, has become the default therapy for most aorto-ostial lesions, although there are unique challenges of stent placement in the aorto-ostial location, such as protrusion of the stent into the aorta precluding

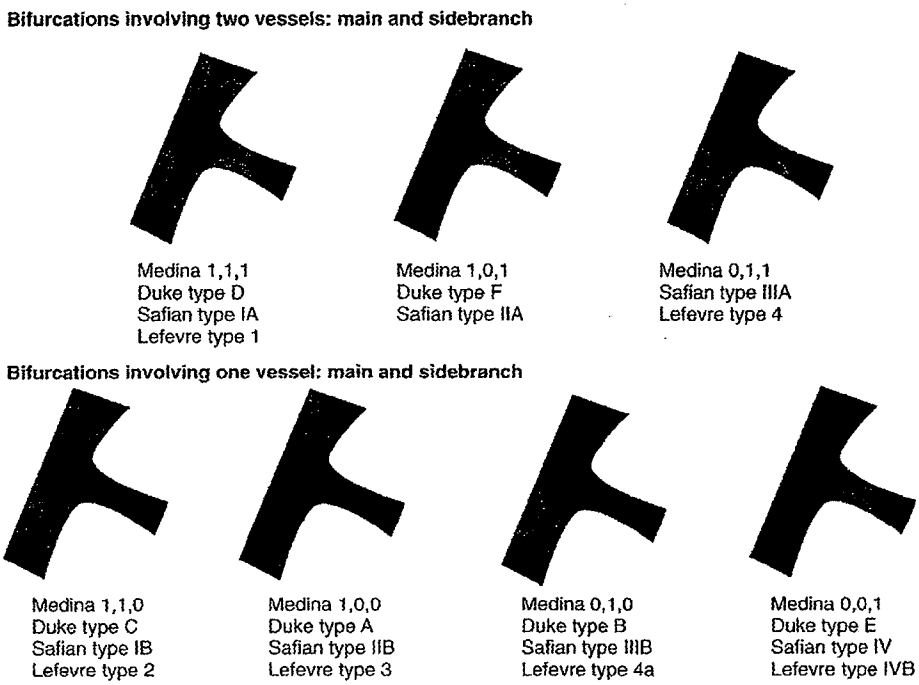


Figure 60-1. Schematic classification system for types of bifurcation stenoses.

subsequent injection catheter engagement, compression, and avulsion of the stent struts into the aorta when new devices such as cutting balloon angioplasty are used to treat ISR.

Isolated nonaorto-ostial stenoses of the left circumflex and left anterior descending coronary arteries[17] and ostial side branch bifurcation lesions are also effectively treated with DES,[18] but they pose unique challenges regarding vessel wall geometry, adequate ostial branch coverage (particularly if there is a narrow angle with the adjacent branch), and plaque shifting causing compromise of the parent or adjacent branch vessels. Whereas stent protrusion into the parent vessel of less than 1 mm is usually well tolerated, stent protrusion to greater degrees precludes treatment of the parent branches.[18] Stent fractures have been reported with more advanced stenting techniques used to treat the parent vessel and ostial side branch stenoses.

Long Lesions

Lesion length may be estimated quantitatively as the "shoulder-to-shoulder" extent of atherosclerotic narrowing greater than 20%, although many clinicians estimate lesion length based on the identification of a "normal to normal" segment, which is usually longer than the length obtained with quantitative methods. Conventional balloon angioplasty of long lesions has been associated with reduced procedural success, particularly when the segment is diffusely diseased (i.e., >20 mm in length), primarily because of the more extensive plaque burden in long lesions.

Stents improve late outcome compared with balloon angioplasty, but stent and lesion length remain the most important predictors of restenosis in the stent era.[19] Coronary stents have been used to treat suboptimal angiographic results ("spot stenting") and dissections after balloon angioplasty of longer lesions, although the "full metal jacket" stent approach to diffuse disease is associated with a higher recurrence rate in the absence of complete stent expansion, particularly in smaller vessels. Overlapping sirolimus-eluting stents provide safe and effective treatment for long coronary lesions.[20]

Bifurcation Lesions

The risk of side branch occlusion in bifurcation lesions relates to the extent of atherosclerotic involvement of the side branch within its origin from the parent vessel, which ranges from 14% to 27% in side branches with ostial involvement. To accurately assess the risk of side branch occlusion and avoid conflicting definitions of side branch and ostial stenosis, a number of classification systems for bifurcation stenoses have been proposed (Fig. 60-1).[21-24]

One stent is preferable to stents in both the parent vessel and the side branch, because subacute thrombosis and restenosis remain higher in bifurcation disease treated with coronary stents in both branches.[25] If two stents are planned for the parent vessel and side branch, a number of stenting techniques are

possible, including simultaneous kissing stents, crush, coulotte, and T stenting. To date, the optimal technique has not been identified, although the use of DESs appears to reduce restenosis compared with bare metal stents. The origin of the side branch is the most common location of failure (recurrence) after bifurcation stenting.[26] A number of dedicated bifurcation stents have been developed to provide adequate vessel coverage[27] and side branch access[28] during stent deployment. Common to all of these strategies is a final "kissing" balloon inflation in the parent vessel and side branch.[29]

Total Occlusion

Total coronary occlusion is identified as an abrupt termination of the epicardial vessel; anterograde and retrograde collaterals may be present and are helpful in quantifying the length of the totally occluded segment. Coronary occlusions are common findings[30] and often lead to the decision to perform coronary bypass surgery rather than PCI in the setting of multivessel disease.[31,32] The success rate for recanalization depends on the occlusion duration and on certain lesion morphologic features, such as bridging collaterals, occlusion length greater than 15 mm, and absence of a "nipple" to guide wire advancement. Although newer technologies and techniques have been used to recanalize refractory occlusions,[33,34] better guide wires and wire techniques have accounted for much of the improvement in crossing success over recent years.[35] Simultaneous coronary injections are sometimes useful for identifying the length of the total occlusion (Fig. 60-2). Once the occlusion has been crossed, coronary stents, including DES,[36,37] have been used to provide the best long-term outcomes.

A key component to the assessment of total occlusion is definition of the collateral grades that provide blood flow to the jeopardized myocardium.[38] The Rentrop classification system includes Rentrop grade 0 (no filling), Rentrop grade 1 (small side branches filled), Rentrop grade 2 (partial epicardial filling of the occluded artery), and Rentrop grade 3 (complete epicardial filling of the occluded artery). Anatomic collaterals summarized by the 26 potential pathways were consolidated into four groups: septal, intra-arterial (bridging), epicardial with proximal takeoff (atrial branches), and epicardial with distal takeoff.[39] Finally, the size of the collateral connection can be quantified as group 0 (no continuous connection between donor and recipient artery), group 1 (continuous threadlike connection ≤0.3 mm), or group 2 (continuous small, branch-like collateral through its course ≥0.4 mm).[39]

Angiographic Complications After Percutaneous Coronary Intervention

Although the frequency of angiographic complications during PCI has been reduced substantially with the use of coronary stents, untoward effects resulting from disruption of the atherosclerotic plaque and embolization of atherosclerotic debris, thrombus, and vasoactive mediators still occurs during 5% to 10% of PCI procedures.

Coronary Dissection

Plaque fracture is an integral component of balloon angioplasty, although significant vessel wall disruption resulting in reduced anterograde flow and lumen compromise is a relatively uncommon occurrence (<3%).[40] The National Heart, Lung, and Blood Institute (NHLBI) coronary dissection criteria categorize the severity of coronary dissection after PCI (Table 60-4), with the prognostic implications of the coronary dissection depending on extension into the media and adventitia, axial length, presence of contrast staining, and effect on anterograde coronary perfusion. It is sometimes difficult to assess the angiographic residual lumen in the presence of coronary dissection because of the frame-to-frame lumen diameter changes seen with two-dimensional imaging; in the setting, intravascular ultrasound (IVUS) may provide a more accurate reflection of the true circumference lumen dimensions. Dissections resulting in a residual area stenosis of 60% or greater by IVUS[41] and those extending more than 5 to 10 mm in axial length are associated with a worse prognosis.

"No-Reflow"

Reduced flow during PCI, also known as "no-reflow," is defined as a reduction in anterograde flow despite a patent lumen at the site of PCI. It occurs during 1% to 5% of PCI procedures. No-reflow is a strong predictor of mortality after PCI.[42] No-reflow is more common (15%) during primary angioplasty for AMI.[43] Predictors of no-reflow include a higher plaque burden, thrombus, lipid pools by IVUS, higher lesion elastic membrane cross-sectional area, preinfarction angina, and Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 on the initial coronary angiogram, among other factors.[44-46] Compared to aspirates obtained from patients without no-reflow, aspirates obtained from patients who developed no-reflow contained more atheromatous plaque and significantly more platelet and fibrin complex, macrophages, and cholesterol crystals.[47] The 30-day mortality rate was significantly higher (27.5%) in patients with combined slow-flow and no-reflow phenomenon than in patients with normal coronary blood flow after PCI (5.3%; $P < .001$).[43] Intracoronary or intragraft nitroprusside,[48] adenosine,[49] verapamil,[50] and nicardipine[51] and aspiration of atherosclerotic debris have each been used to correct the episode of no-reflow.

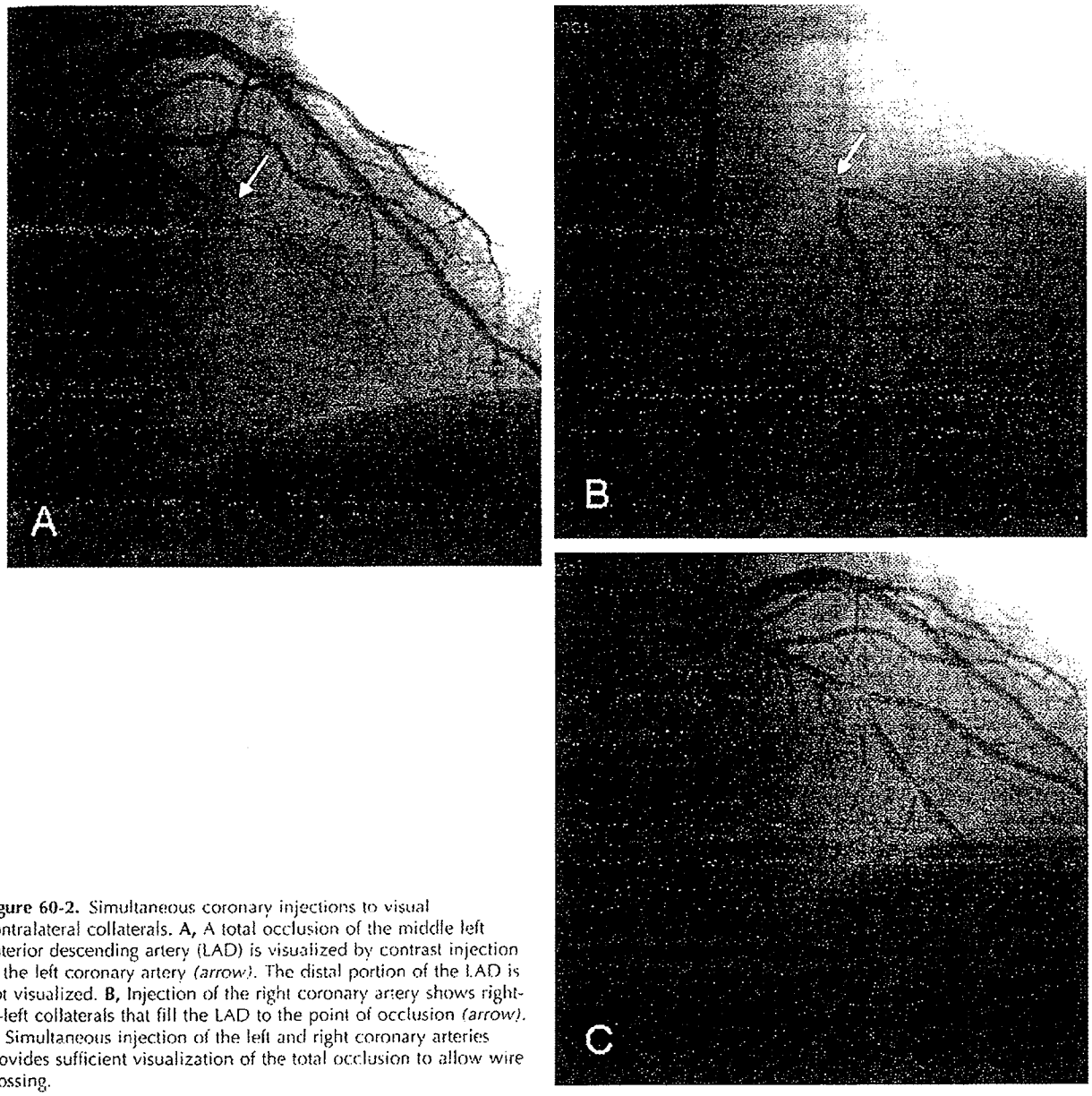


Figure 60-2. Simultaneous coronary injections to visual contralateral collaterals. **A,** A total occlusion of the middle left anterior descending artery (LAD) is visualized by contrast injection in the left coronary artery *(arrow)*. The distal portion of the LAD is not visualized. **B,** Injection of the right coronary artery shows right-to-left collaterals that fill the LAD to the point of occlusion *(arrow)*. **C,** Simultaneous injection of the left and right coronary arteries provides sufficient visualization of the total occlusion to allow wire crossing.

Distal Embolization

Periprocedural myonecrosis provides clinical evidence of distal particulate embolization during PCI. Angiographic distal embolization is defined as the migration of a filling defect or thrombus to distally occlude the target vessel or one of its branches.[52] It occurs in approximately 10% of patients with an AMI undergoing PCI. Embolic complications occur more often in patients with AMI and in patients undergoing balloon angioplasty of SVG lesions, particularly those with recent occlusion.

Coronary Perforation

Coronary perforation is an uncommon (<1%) complication of PCI that is associated with significant morbidity and mortality.[53-57] Coronary perforations are infrequent in patients undergoing balloon angioplasty (0.1%) compared with patients undergoing atheroablative therapy (1.3%; $P < .001$).[54,58] Perforation due to coronary guide wires may manifest late after the procedure. Initial management strategies include prolonged balloon inflation, reversal of anticoagulation, and, in refractory cases, use of PTFE-covered stents.[59-61]

Table 60-4. Standardized Criteria for Postprocedural Lesion Morphology

Feature	Definition
Abrupt closure	Obstruction of contrast flow (TIMI 0 or 1) in a dilated segment with previously documented anterograde flow
Ectasia	A lesion diameter greater than the reference diameter in one or more areas
Luminal irregularities	Arterial contour that has a "sawtooth pattern" consisting of opacification but not fulfilling the criteria for dissection or intracoronary thrombus
Intimal flap	A discrete filling defect in apparent continuity with the arterial wall
Thrombus	Discrete, mobile angiographic filling defect with or without contrast staining
Dissection*	
A	Small radiolucent area within the lumen of the vessel
B	Linear, nonpersisting extravasation of contrast
C	Extraluminal, persisting extravasation of contrast
D	Spiral-shaped filling defect
E	Persistent lumen defect with delayed anterograde flow
F	Filling defect accompanied by total coronary occlusion
Length	Measure end-to-end for type B through F dissections
Staining	Persistence of contrast within the dissection after washout of contrast from the remaining portion of the vessel
Perforation	
Localized	Extravasation of contrast confined to the pericardial space immediately surrounding the artery and not associated with clinical tamponade
Nonlocalized	Extravasation of contrast with a jet not localized to the pericardial space, potentially associated with clinical tamponade
Side branch loss	TIMI 0, 1, or 2 flow in a side branch >1.5 mm in diameter that previously had TIMI 3 flow
Distal embolization	Migration of a filling defect or thrombus to distally occlude the target vessel or one of its branches
Coronary spasm	Transient or permanent narrowing >50% when a <25% stenosis was previously noted

*National Heart, Lung, and Blood Institute classification system for coronary dissection.
TIMI, Thrombolysis in Myocardial Infarction.

The prognosis after coronary perforation depends on the extent of extravasation into the pericardium.[58] A classification scheme has been developed based on angiographic appearance of the perforation, with type I perforations including an extraluminal crater without extravasation, type II perforations containing pericardial or myocardial blushing, and type III perforations having a diameter equal to or greater than 1 mm with contrast streaming and cavity spilling.[58] Type I perforations were associated with no deaths and cardiac tamponade in 8% of patients; type II perforations were associated with no deaths and cardiac tamponade in 13% of cases; and type III perforations were associated with death in 19% and cardiac tamponade in 63% of patients.[58]

Coronary Spasm

Coronary spasm is defined as a transient or sustained reduction in the diameter stenosis by more than 50% in an arterial segment with insignificant (<25%) baseline narrowing. Although coronary spasm may occur in approximately 5% of cases, its frequency has been reduced with the routine use of coronary vasodilators, such as nitroglycerin and calcium channel blockers. Wire straightening of the vessel can mimic coronary spasm.

Abrupt Closure

Abrupt closure during coronary intervention is defined as an abrupt cessation of coronary flow to TIMI 0 or 1; it occurs during 3% to 5% of balloon angioplasty procedures. Abrupt closure may be caused by coronary dissection, embolization, or thrombus formation within the vessel. Its incidence has been markedly reduced with the availability of coronary stents.[62]

Stent Thrombosis

With the addition of a thienopyridine derivative (i.e., ticlopidine or clopidogrel) to aspirin, the incidence of bare metal stent thrombosis within 30 days of the procedure is less than 1%. Predictive factors for stent thrombosis include persistent dissection NHLBI grade B or higher after stenting, greater total stent length, and a smaller final minimal lumen diameter within the stent.[63] DES administered with longer durations (3 to 6 months) of dual antiplatelet therapy have similar stent thrombosis rates to those found with bare metal stents,[64,65] although premature discontinuation of dual antiplatelet therapy has been associated with higher (6% to 29%) stent thrombosis rates.[25,66,67] In addition, diabetes, prior brachytherapy, bifurcation lesions with two stents, AMI, renal failure, lower ejection fraction, and longer stent length have been associated with stent thrombosis.[25,66,67] A recent concern is the occurrence of very late (>1 year) stent thrombosis with the use of DES[68] due to inflammation from the stent.[69,70] The estimated incidence of very late stent thrombosis ranges from 0.2% to 0.6% per year up to 3 years after stent placement. Long-term dual antiplatelet therapy may not be completely protective to prevent stent thrombosis.[66]

The Academic Research Consortium has proposed new criteria for the timing and definitions used to

Table 60-5. Academic Research Consortium (ARC) Stent Thrombosis Definitions

Stent Thrombosis	Definition
Definite	
Angiographic confirmation	TIMI flow grade 0 with occlusion originating in or within 5 mm of stent in the presence of a thrombus *or* TIMI flow grade 1, 2, or 3 originating in or within 5 mm of stent in the presence of a thrombus *AND* at least one of the following criteria within the last 48 hr: New acute onset of ischemic symptoms at rest (typical chest pain with duration >20 min) New ischemic ECG changes suggestive of acute ischemia Typical rise and fall in cardiac biomarkers
Pathologic confirmation	Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved after thrombectomy
Probable	
	Any unexplained death within the first 30 days Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other cause.
Possible	
	Any unexplained death >30 days after intracoronary stenting

ECG, electrocardiographic; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

document stent thrombosis in clinical studies. Timing of stent thrombosis is defined as acute (<24 hours), subacute (24 hours to 30 days), late (30 days to 1 year), and very late (after one year).[71] The categories of definite stent thrombosis, probable stent thrombosis, and possible stent thrombosis have been proposed as a more inclusive and standardized way to characterize the occurrence of this event in patients undergoing stent implantation (Table 60-5).

Restenosis Pattern

When ISR occurs after bare metal stent implantation, the risk of recurrence can be predicted by the pattern of restenosis.[72,73] Using the Mehran classification system, pattern I includes focal (≤10 mm in length) lesions, pattern II is defined as ISR greater than 10 mm within the stent, pattern III includes ISR greater than 10 mm extending outside the stent, and pattern IV is totally occluded ISR.[72] Pattern I can be classified further by the location of the restenosis: Ia, within the stent; Ib, at the edge of the stent; Ic, at the articulation or gap; or Id, multifocal.[72] The need for recurrent target lesion revascularization (TLR) increased with increasing ISR class, from 19% to 35%, 50%, and 83% in classes I through IV, respectively ($P < .001$).[72] Restenosis after DES implantation is generally more focal than after bare metal stent placement,[19,74] and with the sirolimus-eluting stent, it is more commonly seen at the margin of the stent owing to balloon injury that is not covered with stent.[19,75]

Late Aneurysm Formation

Late vessel wall expansion of greater than 20% after PCI has been termed a coronary artery aneurysm. Coronary artery aneurysms, or, more precisely, pseudoaneurysms, are rare findings after balloon angioplasty, atheroablation, and coronary stenting. Coronary artery aneurysms most likely arise from tears or dissection and incomplete healing that compromises vessel wall integrity and results in vessel wall expansion. Coronary artery aneurysms are also rarely (<1%) seen after DES placement, although the pathologic etiology of aneurysms in this setting may relate to expansion of all three layers of the arterial wall owing to inflammation and effects from the cytostatic or cytotoxic drugs and malapposition of the stent struts.[76,77] Under rare circumstances, coronary artery aneurysms can become infected, requiring surgical intervention.[78,79]

Coronary Perfusion

Evaluation of pharmacologic and mechanical methods to reperfuse coronary occlusions in patients with ST-segment elevation myocardial infarction (STEMI) is supported by the development of a reproducible angiographic method to assess the degree of coronary recanalization achieved with these therapies. The TIMI flow grade classification scheme characterizes the extent of coronary recanalization in patients with STEMI treated with systemic thrombolytic agents, and in patients presenting with non-ST-segment elevation myocardial infarction and unstable angina (Table 60-6).[80] The TIMI frame count[81] and the TIMI myocardial perfusion grade were developed to further quantify anterograde flow and assess distal microvascular perfusion.[82]

TIMI Flow Grade Classification Scheme

The TIMI Flow Grade System is a valuable tool for assessing the efficacy of reperfusion strategies in patients with STEMI and for identifying patients at higher risk for an adverse outcome with acute coronary syndromes or undergoing PCI. Several thrombolytic trials have identified an important relationship between 90-minute TIMI flow grade after

Table 60-6. TIMI Flow Grade Classification

Grade	Characteristic
3 (complete reperfusion)	Anterograde flow into the terminal coronary artery segment through a stenosis is as prompt as anterograde flow into a comparable segment proximal to the stenosis. Contrast material clears as rapidly from the distal segment as from an uninvolved, more proximal segment.
2 (partial reperfusion)	Contrast material flows through the stenosis to opacify the terminal artery segment. However, contrast enters the terminal segment perceptibly more slowly than more proximal segments. Alternatively, contrast material clears from a segment distal to a stenosis noticeably more slowly than from a comparable segment not preceded by a significant stenosis.
1 (penetration with minimal perfusion)	A small amount of contrast flows through the stenosis but fails to fully opacify the artery beyond.
0 (no perfusion)	No contrast flow through the stenosis.

Modified from Sheehan FH, Braunwald E, Canner P, et al: The effect of intravenous thrombolytic therapy on left ventricular function: A report on tissue-type plasminogen activator and streptokinase from the Thrombolysis in Myocardial Infarction (TIMI) Phase I Trial. Circulation 1987;72:817-829.

thrombolysis and clinical outcome.[83] In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) angiographic substudy, the mortality rate for patients with TIMI 2 flow (7.4%) was similar to the mortality rate for those with TIMI 0 or 1 flow (8.9%). In contrast, the mortality rate was lowest (4.4%) in patients with TIMI 3 flow.[83]

Despite these important associations, there are a number of limitations of the TIMI classification system. Substantial observer variability has been noted with the TIMI flow grade, with the best agreement between the angiographic core laboratory and clinical centers occurring when the artery is graded as either open or closed (TIMI 0 or 1 flow; kappa value = 0.84).[81] Observer agreement is only moderate when assessing TIMI grade 3 flow (kappa value = 0.55) and is poor in the assessment of TIMI grade 2 flow (kappa value = 0.38). The lack of concordance for determining TIMI flow grade was also shown between experienced angiographic core laboratories. Another limitation of the TIMI flow grade is that it provides ordinal values rather than continuous ones, limiting its statistical power in clinical trials. Furthermore, although TIMI flow grade has classically compared flow in the infarct-related vessel to flow in the "normal" nonculprit artery, flow in the non-infarct-related artery in patients with STEMI is not truly normal compared with flow in patients without STEMI.[84] Difficulties in reproducibly assessing myocardial flow relative to other vessels (e.g., the right coronary artery, or in the setting of total occlusions of the contralateral vessel) led some investigators to modify the definition of "TIMI grade 3 flow" to include opacification of the distal coronary artery within three cardiac cycles.[85] The "three cardiac cycle" definition of TIMI 3 flow results in an absolute rate increase of approximately 10% compared with the original definition.[86] Accordingly, more quantitative measures of anterograde flow were developed.

TIMI Frame Count

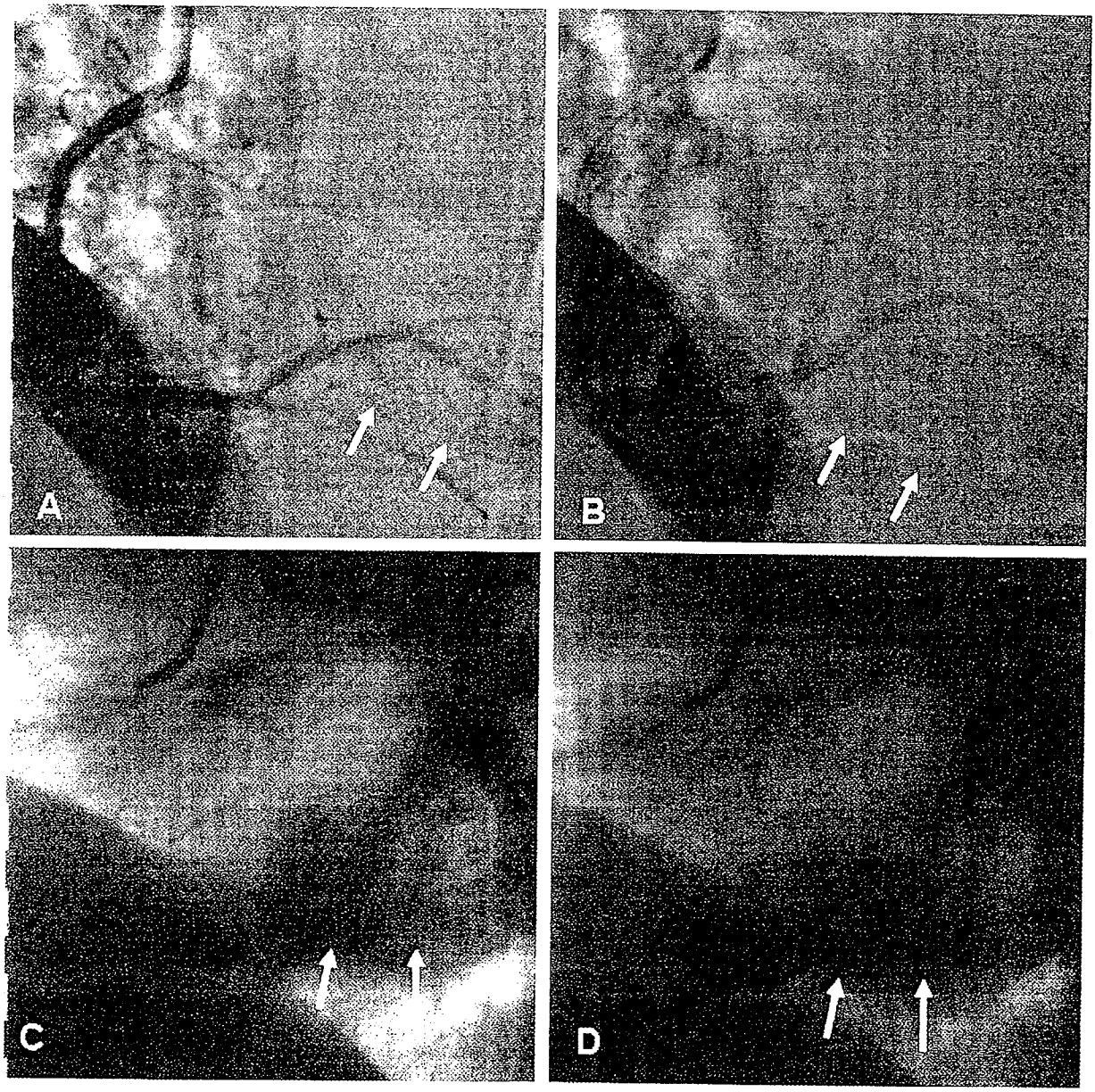
The TIMI Frame Count (TFC) provides a quantitative assessment of the number of frames required for dye to reach standardized distal landmarks, and it may provide a more objective and precise method of estimating coronary blood flow than the TIMI flow grade.[81] The first frame used for TIMI frame counting is defined as the cineframe in which a column of dye touches both borders of the coronary artery and moves forward, and the last frame is characterized as the cineframe in which dye begins to enter (but does not necessarily fill) a standard distal landmark in the artery. The standard distal landmarks for epicardial vessels are the first branch of the posterolateral artery for the right coronary artery; the most distal branch of the obtuse marginal branch in the dye path through the culprit lesion in the circumflex system; and the distal bifurcation, which is also known as the "moustache," "pitch fork," or "whale's tail," in the left anterior descending coronary artery. These frame counts are corrected for the longer length of the left anterior descending coronary artery by dividing the TFC by 1.7 to arrive at the corrected TIMI frame count (CTFC).

The CTFC provides a number of advantages over TIMI flow grades. The CTFC is quantitative rather than qualitative, objective rather than subjective, and a continuous rather than a categorical variable. Observer variability is also substantially less with TFC measurements compared with TIMI flow grades.[81] Furthermore, although it has traditionally been assumed that basal flow in nonculprit arteries in the setting of AMI after thrombolysis is "normal," it is now appreciated that basal flow in the uninvolved artery is abnormal using the CTFC.[84]

The more objective CTFC has also been related to clinical outcomes.[82] Flow in the infarct-related artery in survivors of STEMI was significantly faster than in patients who died; mortality increased by 0.7% for every 10-frame rise in the CTFC ($P < .001$).[82] None of the patients in the TIMI studies who had a CTFC less than 14 (hyperemic or TIMI grade 4 flow) died within the first 30 days. In another series of patients undergoing PCI, none of the 376 patients with a CTFC less than 14 after angioplasty died, underscoring the fact that, within the subgroup of patients with "normal flow," there may be further subgroups with even better flow.

TIMI Myocardial Perfusion Grade

.: is now apparent that epicardial flow does not necessarily imply tissue-level or microvascular perfusion. These findings led to the development of the TIMI Myocardial Perfusion Grade (TMPG) (Fig. 60-3; Table 60-7), which has been shown to be a multivariate predictor of mortality in AMI.[82] The TMPG permits sk stratification even within epicardial TIMI grade flow. That is, despite achieving normal TIMI grade 3 flow after reperfusion therapy, patients with diminished microvasculature perfusion (TMPG 0 or 1) have a persistently elevated mortality rate of 5.4% compared with patients with both TIMI grade 3 flow and TMPG 3, who have a mortality rate less than 1%.[82] Accordingly, the TIMI flow grades and the TMPGs can be combined to identify a group of patients at "very low" or "very high" risk for mortality after STEMI. Those patients with both TIMI grade 3 flow and TMPG 3 flow had a mortality rate of 0.7%, whereas patients with both TIMI grade 0 or 1 and TMPG 0 or 1 flow had a mortality rate of 10.9%.



gure 60-3. Thrombolysis in Myocardial Infarction (TIMI) myocardial perfusion grade using digital subtraction angiography. Perfusion grade 0 is characterized by the absence of the typical "ground-glass" filling of the distal vascular bed during coronary injection (A) and ashout (B). Perfusion grade 1 is demonstrated by persistent contrast staining at the beginning (C) and end (D) of the coronary injection.

Continued

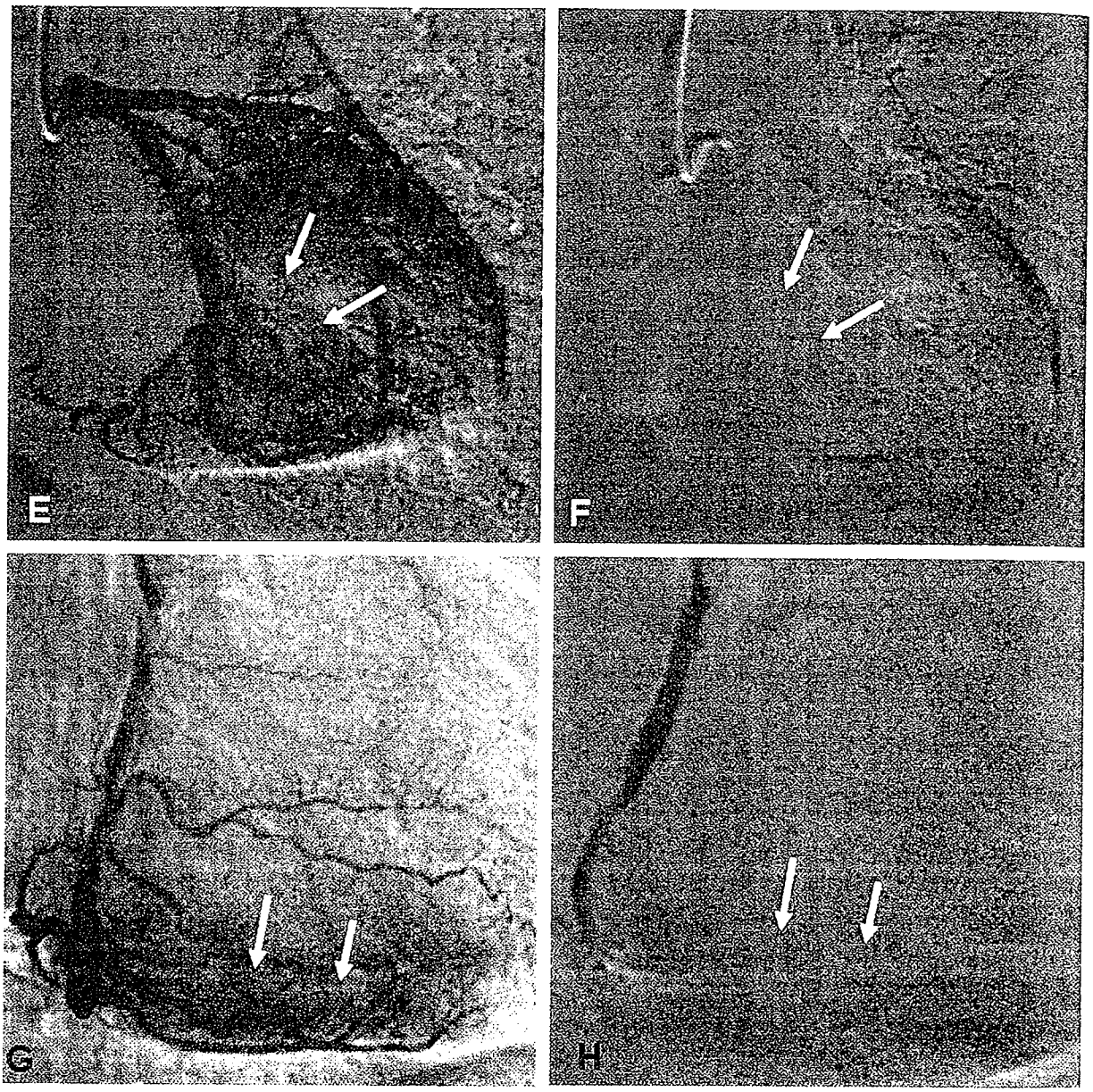


Figure 60-3, cont'd Perfusion grade 2 is manifested by a very prominent contrast appearance at the end of coronary injection (**E**) that washes out at the end of the contrast injection (**F**). Perfusion grade 3 is shown as a normal ground-glass appearance of the distal vascular bed at the end of the contrast injection (**G**) that washes out at the end of the injection (**H**).

Another approach to assess myocardial perfusion is to use digital subtraction angiography (DSA) to quantitatively characterize the kinetics of dye entering the myocardium during contrast angiography. DSA is performed at end-diastole by aligning cine-frame images taken before dye fills the myocardium with those taken at the peak of myocardial filling to subtract spine, ribs, diaphragm, and epicardial artery. A representative region of the myocardium that is free of overlap by epicardial arterial branches is sampled to determine the increase in the gray-scale brightness of the myocardium when it first reached its peak intensity. The circumference of the myocardial blush is measured using a hand-held planimeter. The number of frames required for the myocardium to first reach its peak brightness is converted into time (seconds) by dividing the frame count by 30 (for images acquired at 30 frames per second). The rate of rise in brightness (gray-scale change per second) and the rate of growth of blush in circumference (centimeters per second) can then be calculated. Using DSA, microvascular perfusion was reduced in

Table 60-7. TIMI Myocardial Perfusion Grades

Grade	Characteristic
3	Normal entry and exit of dye from the microvasculature. There is a ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that clears normally and is either gone or mildly or moderately persistent at the end of the washout phase (approximately three cardiac cycles), similar to an uninvolved artery. Blush that is of only mild intensity throughout the washout phase but fades normally is also classified as grade 3.
2	Delayed entry and exit of dye from the microvasculature. There is a ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that is strongly persistent at the end of the washout phase (i.e., dye is strongly persistent after three cardiac cycles of the washout phase and either does not diminish or only minimally diminishes in intensity during washout).
1	Slow entry of dye into but failure to exit the microvasculature. There is a ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that fails to clear from the microvasculature, and dye staining is present on the next injection (approximately 30 sec between injections).
0	Failure of the dye to enter the microvasculature. There is either minimal or no ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit artery, indicating lack of tissue-level perfusion.

AMI patients compared to normal patients, as demonstrated by a reduction in peak brightness (gray-scale peak), the rate of rise in brightness, the blush circumference, and the rate of growth of blush in circumference.[87]

Coronary Flow Velocity

Absolute flow velocity can be measured using PCI guidewire velocity.[88] With this technique, the guidewire tip is placed at the coronary landmark after PCI, and a Kelly clamp is placed on the guidewire at the point at which it exits the Y-adapter. The guidewire tip is then withdrawn to the catheter tip, and a second Kelly clamp is placed on the wire where it exits the Y-adapter. The distance between the two Kelly clamps outside the body is measured as the distance between the catheter tip and the anatomic landmark inside the body. Velocity (centimeters per second) may be calculated as this distance (centimeters) divided by the product of the TFC (frames) and the film frame speed (frames per second). Flow (milliliters per second) may be calculated by multiplying velocity and the mean cross-sectional lumen area (square centimeters) along the length of the artery to the TIMI landmark. In a series of 30 patients undergoing PCI, velocity increased from 13.9 ± 8.5 cm/second before PCI to 22.8 ± 9.3 cm/second after PCI ($P < .001$). For all 30 patients, flow doubled from 0.6 ± 0.4 mL/second before PCI to 1.2 ± 0.6 mL/second after PCI ($P < .001$). In the 18 patients with TIMI grade 3 flow both before and after PCI, flow increased 86%, from 0.7 ± 0.3 to 1.3 ± 0.6 mL/second ($P = .001$).

QUANTITATIVE ANGIOGRAPHY

Quantitative coronary angiography (QCA) is most commonly performed using automated arterial contour detection, although videodensitometry and digital parametric imaging have also been tried with limited success. Whereas "online" QCA is somewhat cumbersome to use in the catheterization laboratory, "offline" QCA has proved to be valuable for research investigation in determining the effect of new drugs and devices on lumen dimensions early and late after PCI. Notably, for clinical decision-making in intermediate lesions, neither trained visual estimates or online quantitative angiography is a substitute for precise physiologic measurements of stenosis severity, such as fractional flow reserve or coronary Doppler measurements.[89]

Nonquantitative Estimates of Lesion Severity

Virtually every interventionalist uses an "eyeball" estimate for determining angiographic stenosis severity, although these visual estimations of lesion severity are of limited value for research studies because of substantial observer-to-observer variability. Blinded review of cineangiograms by experienced cardiologists found that the average visual diameter stenosis was 85% before PCI (versus 68% using quantitative methods) and 30% after PCI (versus 49% using quantitative methods); these differences correspond to a 200% error in the estimation of percent diameter stenosis.[90] Visual estimates of stenosis severity also result in some values (e.g., 90% to 99% diameter stenosis) that are physiologically untenable for anterograde flow. Inherent overestimation and underestimation visual stenosis severity can be overcome by retraining the clinician's eye.

A more quantitative approach to the assessment of lesion severity uses hand-held or digital calipers to estimate quantitative diameters and percent diameter stenosis. Angiographic images are magnified, and calibration is performed by measuring the known dimensions of the diagnostic or guiding catheter using digital calipers. The observer then visually identifies the lumen border using the calipers, and a calibration factor is obtained to determine absolute coronary dimensions. Properly applied, this method appears to correlate weakly with automated edge-detection algorithms. If caliper measurements are obtained from nonmagnified images, the correlation with automated edge-detection algorithms is less accurate.

Computer-Assisted Quantitative Coronary Angiography

QCA was initiated almost 30 years ago by Brown and colleagues, who magnified 35-mm cineangiograms obtained from orthogonal projections and hand-traced the arterial edges on a large screen. After computer-assisted correction for pincushion distortion, the tracings were digitized and the orthogonal projections were combined to form a three-dimensional representation of the arterial segment, assuming an elliptical geometry. Although the accuracy and precision were enhanced compared with visual methods, the time needed for image processing limited the clinical use of this method.

Several automated edge-detection algorithms were then developed and applied to directly acquired digital images or to 35-mm cinefilm digitized using a cine-video converter. Subsequent iterations of these first-generation devices used enhanced microprocessing speed and digital image acquisition to render the end-user interface more flexible and substantially shortened the time required for image analysis.

QCA is divided into several distinct processes, including film digitization (when applicable), image calibration, and arterial contour detection (Fig. 60-4). For processing 35-mm cinefilm, a cine-video converter is used to digitize images into a 512 × 512 (or larger) × 8-bit pixel matrix. Optical (preferably) or digital magnification results in an effective pixel matrix up to 2458 × 2458. For estimation of absolute coronary dimensions, the diagnostic or guiding catheter usually serves as the scaling device. In general, a nontapered segment of the catheter is selected, and a centerline through the catheter is drawn. Linear density profiles are then constructed perpendicular to the catheter centerline, and a weighted average of the first and second derivative functions is used to define the catheter edge points. Individual edge points are then connected using an automated algorithm, outliers are discarded, and the edges are smoothed. The diameter of the catheter is then used to obtain a calibration factor, expressed in millimeters per pixel. The injection catheter dimensions may be influenced by whether contrast or saline is imaged within the catheter tip and by the type of material used in catheter construction. As the high-flow injection catheters have been developed, more quantitative angiographic systems have been using contrast-filled injection catheters for image calibration. The automated algorithm is then applied to a selected arterial segment: absolute coronary dimensions are obtained from the minimal lumen diameter (MLD) reference diameter, and, from these, the percent diameter stenoses are derived. For most angiographic systems, interobserver variabilities are 3.1% for diameter stenosis and 0.10 to 0.18 mm for MLD for cineangiographic readings; variabilities are slightly higher (<0.25 mm) for repeated analyses of the digital angiograms owing to the slightly lower resolution compared with cineangiography. The two most commonly used QCA systems are described.

Cardiovascular Angiography Analysis System

The Cardiovascular Angiography Analysis System (CAAS, Pie Data Medical B.V., Maastricht, The Netherlands) is a QCA system developed for offline cineangiographic analysis (see Fig. 60-2). The edge-detection algorithm incorporates an optional correction for pincushion distortion; its edge detection uses a weighted (50%) sum of the first and second derivatives of the mean pixel density; and it applies minimal cost criteria for smoothing of the arterial edge contours. In addition to reporting a interpolated reference diameter and an MLD, a subsegment analysis provides mean, minimum, and maximum subsegment diameters. Specific reporting algorithms have been developed for DESs, for patients undergoing radiation brachytherapy, and for those undergoing peripheral intervention.

Coronary Measurement System

Specific features of the Coronary Measurement System (CMS, MEDIS, Leiden, The Netherlands) include two-point user-defined centerline identification, arterial edge detection using a weighted (50%) sum of the first and second derivatives of the mean pixel density, arterial contour detection using a minimal cost matrix algorithm, and an "interpolated" reference vessel diameter. One limitation of the minimal cost algorithm used with the first-generation CMS system (as well as the CAAS-II system) has been its inability to precisely quantify arterial lumen contours characterized by abrupt changes. The CMS-GFT is an algorithm that is not restricted in its search directions, incorporating multidirectional information about the arterial boundaries for construction of the arterial edge that is suitable for the analysis of complex coronary artery lesions. Specific reporting algorithms have been developed for bifurcation lesions (Fig. 60-5), for DESs (Fig. 60-6), patients undergoing radiation brachytherapy (Fig. 60-7), and for those undergoing peripheral intervention.

Factors Contributing to Variability Using Quantitative Coronary Angiography

Variability associated with measurements of MLD and reference diameter is affected by a number of factors, including (1) the biologic differences among lumen diameters (e.g., reference vessel size, vasomotor tone, thrombus); (2) inconsistencies in radiographic image acquisition parameters (e.g., quantum mottling, out-of-plane magnification, foreshortening); and (3) angiographic measurement variability (e.g., frame selection, factors affecting the edge-detection algorithm) (Table 60-8). These factors should be controlled in order to improve the overall diagnostic accuracy of QCA.

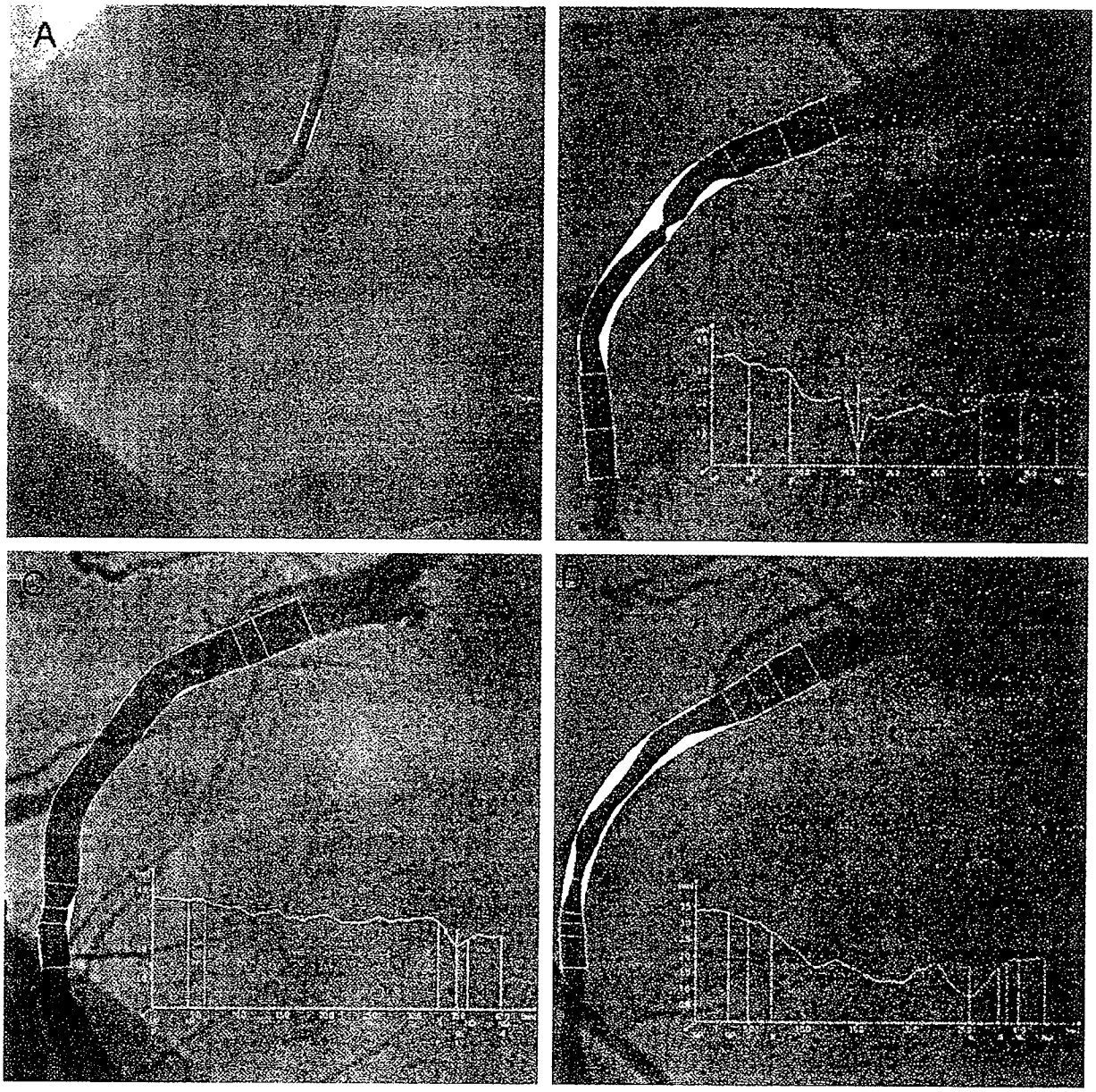


Figure 60-4. Quantitative coronary angiography. A, Image calibration is performed using the nontapered portion of the injection catheter as the calibration source. B, The automated edge detection algorithm (CMS, Leiden, The Netherlands) is applied to the arterial contour, and the minimal lumen diameter (MLD) is identified. A diameter function profile curve *(insert)* shows the diameters of the vessel along the length of the analysis segment. C, After coronary stent placement, the identical length of artery is analyzed to provide an assessment of the lumen improvement. D, At the time of angiographic follow-up, the location of late lumen loss along the length of the analysis segment is identified.

Biologic Variability

Studies that include a wide range of vessel sizes have more biologic variability in vessel diameter (as reflected in the standard deviation of the measurements) than those that are more restrictive in their inclusion criteria. Vasomotor tone may also affect the reference vessel size, resulting in distal vasoconstriction and vasospasm that dynamically affect the arterial diameter in paired measurements. Transient maximum coronary vasodilation may be achieved with intracoronary (50 to 200 μg), intravenous (>10 μg/min), or sublingual (0.4 to 0.8 mg) nitroglycerin.

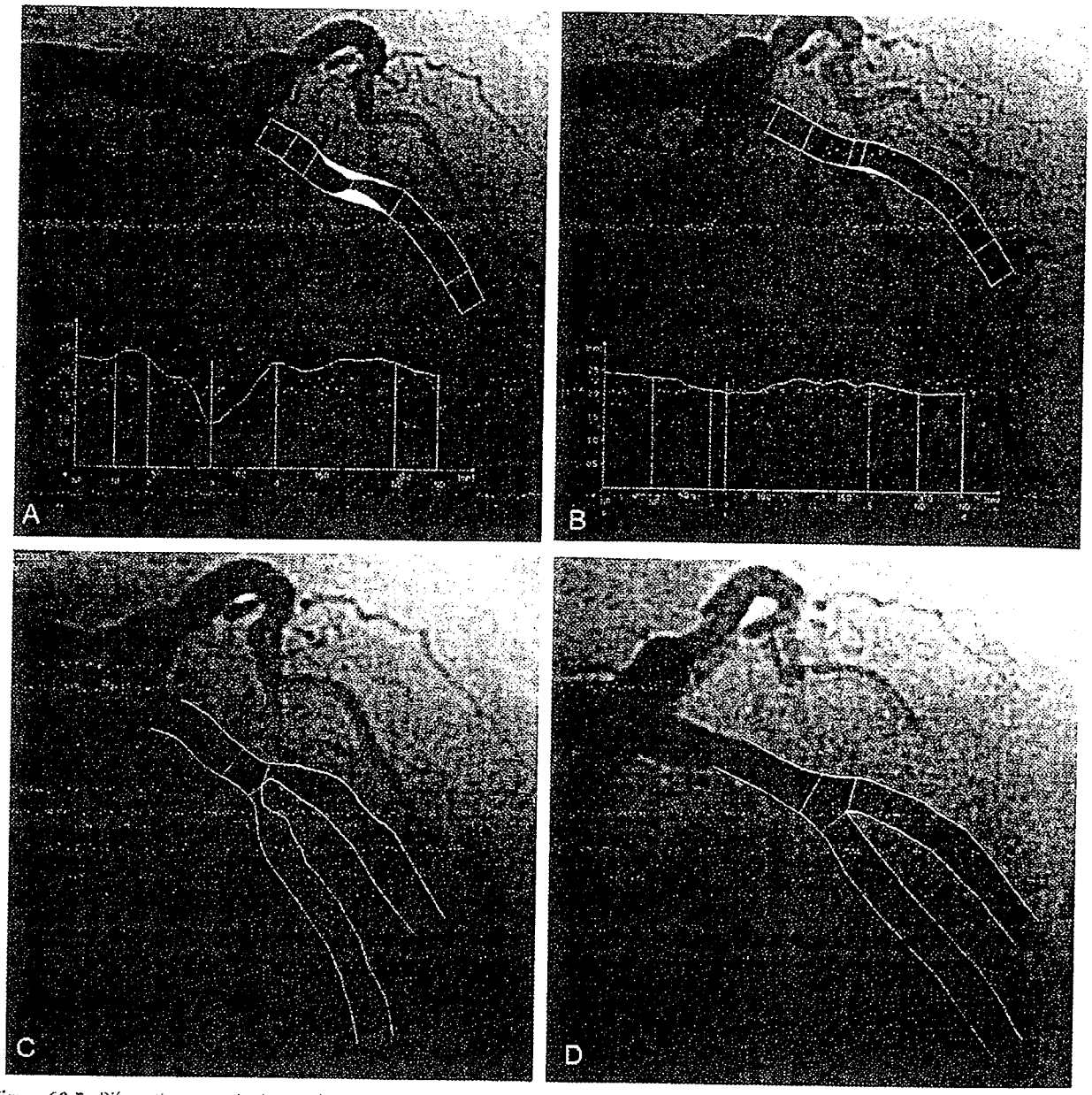


Figure 60-5. Bifurcation quantitative analysis. Quantitative angiographic analysis of bifurcation lesions is complicated by the difficulty in identifying minimal lumen diameter (MLD) at the site of vessel branching. Three methods of bifurcation analysis have been employed: conventional quantitative angiography separately applied to each branch (**A**, before intervention; **B**, after intervention); application of the edge algorithm to both branches (**C**, before intervention; **D**, after intervention); and beginning the analysis at the ostium of the branch (**E**, before intervention; **F**, after intervention).

Acquisition Variability

Acquisition factors that affect variability include cardiac and respiratory motion artifact, vessel foreshortening, inadequate filling of the coronary artery ("streaming"), overfilling of the aortic cusp with contrast, and failure to separate overlapping branch vessels from the stenosis. These factors may lead to either overestimation or underestimation of lesion severity. Out-of-plane magnification and pincushion distortion may also contribute to small errors in angiographic imaging. For sequential studies, use of the identical angiographic imaging laboratory allows replication of the x-ray generator, tube, and image intensifier parameters. With the introduction of digital imaging and archiving, image compression has raised potential problems with the quality of image quality for analysis. The standard Digital Imaging and Communications in Medicine (DICOM) 2:1 JPEG lossless compression has become the

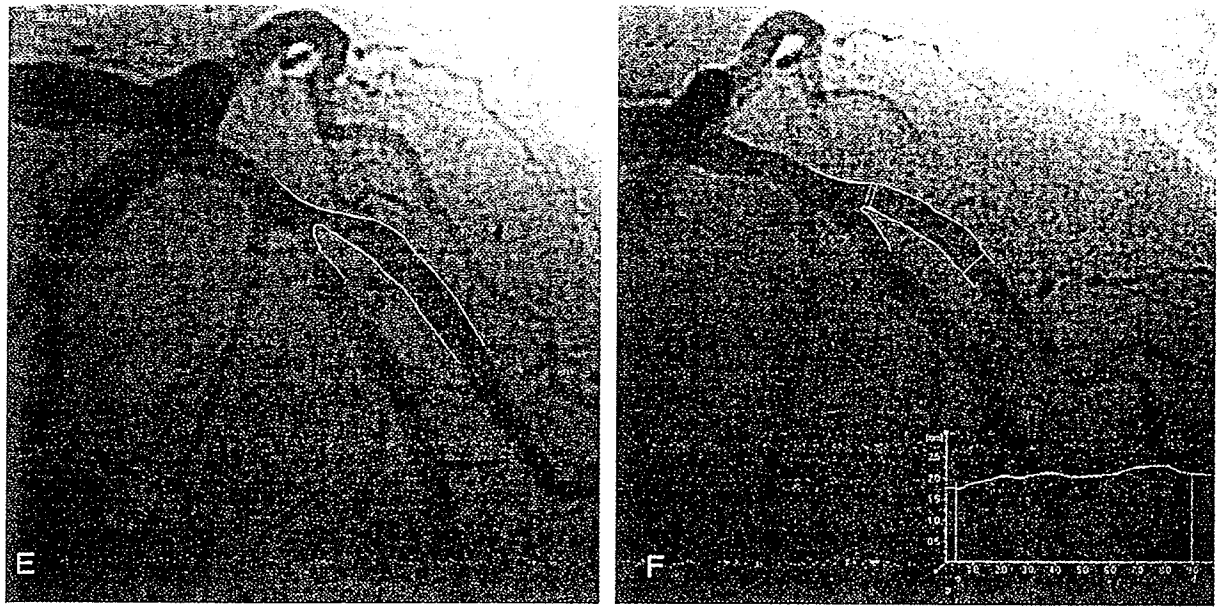


Figure 60-5, cont'd

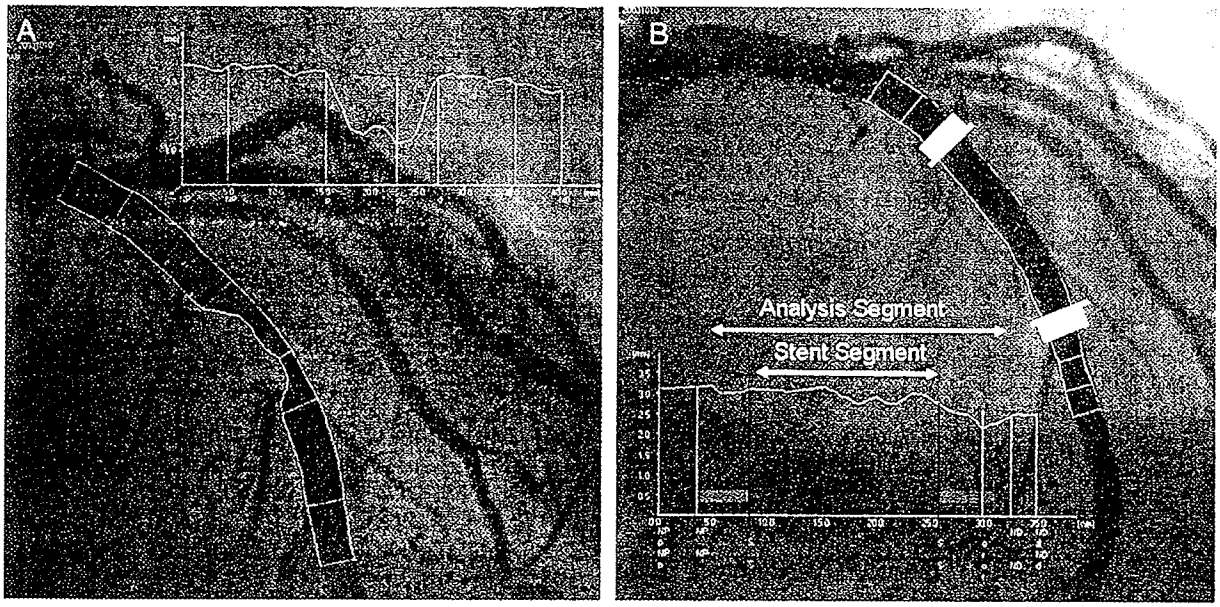


Figure 60-6. Drug-eluting stent quantitative angiographic analysis. A, Quantitative angiography is performed on a focal stenosis in the midportion of the left anterior descending coronary artery (LAD). B, After placement of a drug-eluting stent, the proximal and distal portions of the stent are identified *(solid bars)*. A 5-mm proximal and distal edge is also analyzed *(shaded boxes)*. From these measurements, the minimal lumen diameters within the stent ("stent" segment) and within the region of analysis ("analysis" segment) are identified.

industry standard for image storage and transfer and requires approximately 500 Mbytes of storage for each imaging study. The effect of image compression and decompression on image quality was evaluated by a joint task force of the American College of Cardiology and European Society of Cardiology using Joint Photographic Experts Group (JPEG) images at compression ratios of 1:1 (uncompressed), 6:1, 10:1, and 16:1.[91] The intraobserver analysis showed significant systematic and random errors in the calibration factor at JPEG compression ratios of 10:1 and higher, and therefore these should not be used in

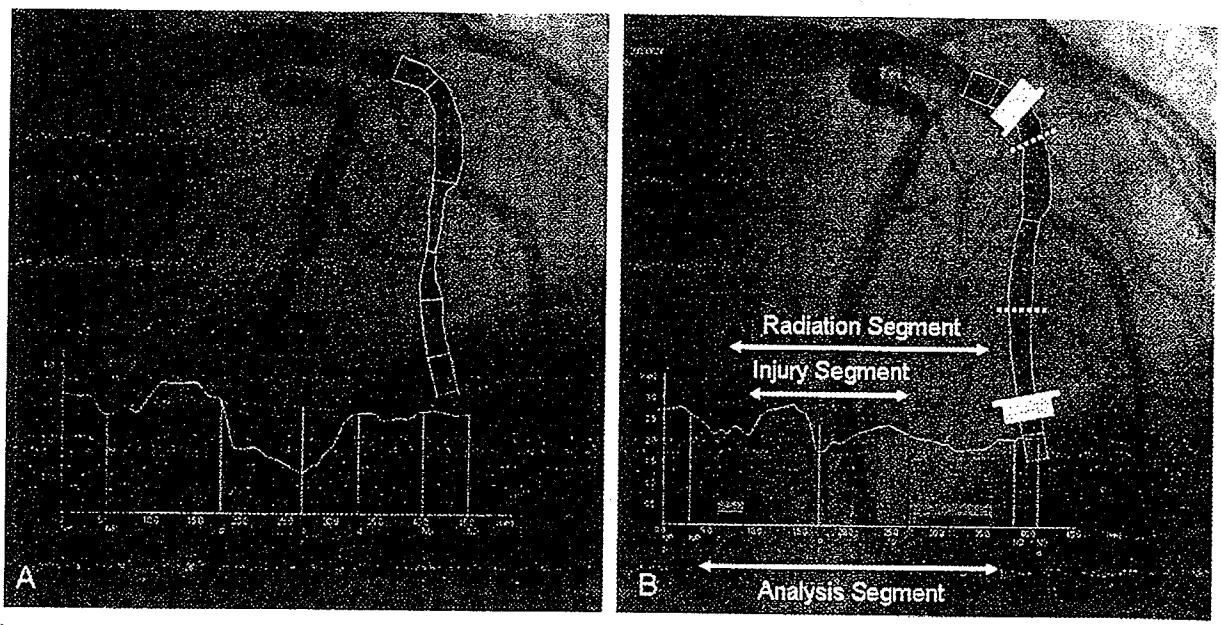


Figure 60-7. Brachytherapy analysis. **A,** Quantitative angiography is performed on a focal stenosis in the midportion of the left anterior descending coronary artery (LAD). **B,** After balloon angioplasty, the proximal and distal portions of the balloon injury are identified *(dashed lines)*. After radiation brachytherapy, the proximal and distal portion of the radiation injury are identified *(solid lines)*. A 5-mm proximal and distal edge of the radiation zone is also analyzed *(shaded boxes)* to identify the "edge effect." From these measurements, the minimal lumen diameters within the segment of balloon injury ("injury" segment), the segment of radiation injury ("radiation" segment), and within the region of analysis ("analysis" segment) are identified. The shaded portion in the diameter function profile curve *(insert)* represents the region of the artery that was treated with radiation but was not injured with the balloon.

Table 60-8. Correctable Sources of Imaging Error during Acquisition

Source of Error	Potential Corrections
Biologic variation in lumen diameter	
Vasomotor tone	Nitroglycerin, 100-200 μg intracoronary every 10 min
Variations in image acquisition	
Single Studies	
Vessel motion	
Cardiac	End-diastolic/end-systolic cineframe
Respiration	Breath-holding
Vessel foreshortening	Obtain multiple angiographic projections
Insufficient contrast injection	Use 7- or 8-Fr large, high-flow catheters
Branch vessel overlap	Obtain multiple angiographic projections
Pincushion distortion	Image objects in center of image
Sequential Studies	
X-ray generator (pulse width/dose/beam quality)	Repeat study in same imaging laboratory
X-ray tube (focal spot/shape/tube current)	As above
Image intensifier (magnification/resolution)	As above
Differences in angles and gantry height	Record gantry height/angle/skew on worksheet
Image calibration	Use measured catheter diameter
Errors in image analysis	
Electronic noise	Recursive digitization and frame averaging
Quantum noise	Spatial filtering of digital image data
Automated edge-detection algorithm	Minimize observer interaction
Selection of reference positions	Interpolated or averaged normal segment
Identification of lesion length	Use of side branches, other landmarks
Frame selection	End-diastolic frame showing "worst" view

QCA clinical research studies.[91] Similar issues exist for the analysis of S-VHS video tapes with substantial loss of image resolution. Flat panel image acquisition does not affect the quality of QCA.[92]

Measurement Variability

Analysis of two or more orthogonal projections permits a more accurate assessment of the physiologic significance of lesion severity, although a second, technically suitable projection in many cases is unavailable owing to vessel foreshortening, overlap, and poor image quality. If orthogonal projections are not available, analyses of the "worst-view" projection may provide sufficiently accurate information for clinical studies. Herrington and colleagues[93] used a components-of-variance model to show that the process of acquiring and performing QCA on selected cineframes accounted for 57% of the total measurement variability, whereas day-to-day variations in the patient, procedure, and equipment accounted for 30% of total variability. Frame selection accounted for the remaining 13% of total variability. When direct digital angiography is performed and random errors associated with noise in the cine-video pathway are eliminated, frame selection may be a much more important contributor to overall measurement variability. Frame selection has been associated with substantial interobserver variability, and the frame demonstrating the sharpest and tightest view of the stenosis should be used.

Automated QCA systems differ with respect to the preferred method of calibration, location of the arterial border, and construction of its contour; use of minimal cost or "smoothing" algorithms; and selection of normal "reference" segments. Edge-detection algorithms that identify the arterial edge using a 50% weighted threshold of the first- and second-derivative extrema may produce systematically larger reference and obstruction diameters than those using a 75% weighted value (weighted toward the first-derivative extremum) or the first-derivative extremum itself. These systematic differences may also affect the accuracy and reproducibility of the absolute and relative angiographic measurements. Accordingly, each angiographic core laboratory should independently determine its own variabilities during the performance of QCA studies, potentially permitting standardization of techniques among different core laboratories.

Quantitative Angiographic Indices

Early and late angiographic results after PCI have been described using a number of QCA criteria. Coronary stents provide a superior residual lumen compared with balloon angioplasty, but they may result in higher amounts of late intimal hyperplasia (and late lumen loss) than is seen after balloon angioplasty. The net balance is that stents provide a net larger late angiographic result.

Angiographic Success

The change in MLD that occurs immediately after PCI is called the *acute gain* (in millimeters), and the loss of MLD that occurs during the follow-up period is defined as the *late loss* (in millimeters). Relative changes that occur in the percent diameter stenosis are provided by the following relationship: % diameter stenosis = (1 – [MLD/Reference Diameter]) × 100. Traditionally, angiographic success after PCI has been defined as the achievement of a less than 50% residual diameter stenosis,[1] which is most often associated with at least 20% improvement from the baseline diameter stenosis as well as symptom improvement. With the advent of coronary stents and the determination that stent thrombosis was associated with a suboptimal initial angiographic result, a more contemporary definition of angiographic "stent success" was the attainment of a less than 20% residual diameter stenosis within the stent, although higher (up to 20% to 30%) "inflow" or "outflow" diameter stenosis may be present owing to residual plaque at the stent margins. Although the documented disparity between visual and quantitative estimates of angiographic success remains a challenge for self-reporting registries that describe procedural outcomes,[1] there has been documented improvement in angiographic success rates over the past decade with the more widespread use of coronary stents.[94]

Binary Angiographic Restenosis

A number of binary criteria have been used to describe angiographic restenosis after PCI. Binary angiographic restenosis is best defined as a 50% or greater diameter stenosis at follow-up, although a number of other dichotomous criteria have been used (e.g., loss of >50% of the initial gain, loss in MLD of ≥0.72 mm). Binary angiographic restenosis after DES placement may occur within the stent ("in-stent" restenosis), within the 5-mm margins of the stent ("edge" restenosis), or within the segment between the proximal and distal reference segments ("in-segment" or "in-lesion" restenosis).

Late Lumen Loss

The long-term success of PCI can be measured by several other QCA parameters. Serial QCA studies have shown that there is an approximate 0.50-mm reduction in lumen diameter that develops within 3 to 6 months after balloon angioplasty, although angiography cannot differentiate whether this reduction in lumen diameter is due to intimal hyperplasia or arterial remodeling (or constriction). Lumen loss after balloon angioplasty follows a near-gaussian distribution. Because there is little or no arterial remodeling after bare metal stent placement, late lumen loss after stent placement is primarily due to intimal hyperplasia, and angiographic estimates of volumet-

ric percent volume obstruction have been well correlated with intravascular ultrasound measurements of intimal hyperplasia.[95]

The distribution of late luminal loss after placement of DES is unlike the distribution of late lumen loss noted after bare metal stent placement, with a narrowing variance (i.e., standard deviation) due to the reduced tissue growth and a rightward skewedness of the late lumen loss histogram,[96] suggesting an "all-or-none" response to the DES.[97] The patient-based relationship between late lumen loss and TLR was examined in 1314 patients with de novo lesions who were treated with bare metal or paclitaxel-eluting stents.[98] In this analysis, the relationship between late lumen loss and TLR was monotonic and curvilinear,[98] with the likelihood of TLR not exceeding 5% until the analysis segment late loss was greater than 0.5 mm, and not exceeding 10% until late loss was greater than 0.65 mm.[98] At lower magnitudes of late lumen loss, there was a very small incremental increase in the occurrence of TLR; with higher degrees of late lumen loss, the late loss–TLR relationship was steep and almost linear.[98] The rate of TLR was related not only to median late loss but also to measures of its statistical distribution. Specifically, TLR increased with lack of homogeneous biologic response, manifested by greater variance (i.e., higher standard deviations) and greater right skewedness of the late lumen loss histogram.[98]

To correct for the rightward skewedness and to develop better predictive models of restenosis, an optimized power transformation was applied to data from patients enrolled in two sirolimus-eluting stent trials to predict binary angiographic restenosis rates and compare them with observed restenosis rates.[99] The mean in-stent late loss was 0.17 ± 0.45 mm after sirolimus-eluting stent placement and 1.00 ± 0.70 mm after bare metal stent placement. If a normal distribution was assumed, late loss accurately estimated in-stent binary angiographic restenosis for the bare metal stent (predicted 35.4% versus observed 35.4%) but underestimated the binary restenosis rate in the sirolimus-eluting stent arm (predicted 0.6% versus observed 3.2%).[99] Power transformation improved the reliability of the estimate in the sirolimus arm (predicted 3.2% versus observed 3.2%).[99] In contrast, another study did not confirm the value of the power transformation as a predictor of binary angiographic restenosis.[100]

To formally evaluate four potential angiographic surrogate markers for TLR by applying well-defined criteria of surrogacy to an extensive database of randomized DES trials, Pocock and colleagues analyzed 11 multicenter, prospective randomized stent trials in 5381 patients with a single treated lesion and follow-up angiography.[101] Based on four surrogate criteria, late loss and percent diameter stenosis strongly predicted the risk of TLR, with in-segment percent diameter stenosis being the most highly predictive (c statistic ~0.95). Whereas late loss as a surrogate was dependent on vessel size, percent diameter stenosis was independent of vessel size. Differences in TLR rates for bare metal and drug eluting stents were fully explained statistically by their differences in late loss and percent diameter stenosis. However, because of the curvilinearity of the logistic model, trials comparing two effective DESs can have significant differences in mean late losses and percent diameter stenosis but negligible expected differences in TLR risk. Others have suggested a stronger relationship between late loss and TLR for comparative DES trials,[102] but whether late lumen loss will serve as a meaningful surrogate end point in DES comparative trials remains controversial.

Quantitative Coronary Angiography in Patients Undergoing Brachytherapy

New technologies, such as radiation brachytherapy, may cause injury at the margin of the treated segment, resulting in "edge" restenosis in regions that were not initially narrowed. Contemporary QCA analyses are performed to identify each of these regional changes in MLD to analyze the local biologic effects of therapy. Radiation coverage may be inadequate in regions of balloon injury ("geographic miss"), or it may have an independent effect on the lumen diameter in regions that are not injured with a balloon catheter ("geographic extension").[103] These quantitative methods have allowed elucidation of the biologic effects of radiation for the treatment of ISR.

Limitations of Quantitative Coronary Angiography

The ability of QCA to accurately detect the presence and severity of coronary atherosclerosis is limited by several factors. Compensatory arterial dilation occurs during the early stages of coronary atherosclerosis, resulting in a preserved coronary lumen despite the presence of significant coronary atherosclerosis. Routine coronary angiography can accurately measure the arterial lumen but is relatively insensitive for the detection of arterial wall atherosclerosis, circumferential plaque distribution, vessel wall calcification, or lumen dimensions after stent implantation.

Coronary angiography is limited to a lesser extent by radiographic factors, such as cardiac motion, pincushion distortion, and quantum mottling; most analysis systems have difficulty discriminating values less than 1.0 mm, owing to limitations of radiographic imaging of small objects (e.g., veiling glare, point spread function). Newer methods incorporating adaptive simultaneous coronary border detection have been developed to more accurately assess smaller vessel dimensions.

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Clinical Investigation and Reports

Inhibition of Restenosis With β-Emitting Radiotherapy

Report of the Proliferation Reduction With Vascular Energy Trial (PREVENT)

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Background—Intracoronary γ- and β-radiation have reduced restenosis in animal models. In the clinical setting, the effectiveness of β-emitters has not been studied in a broad spectrum of patients, particularly those receiving stents.

Methods and Results—A prospective, randomized, sham-controlled study of intracoronary radiotherapy with the β-emitting ^{32}P source wire, using a centering catheter and automated source delivery unit, was conducted. A total of 105 patients with de novo (70%) or restenotic (30%) lesions who were treated by stenting (61%) or balloon angioplasty (39%) received 0 (control), 16, 20, or 24 Gy to a depth of 1 mm in the artery wall. Angiography at 6 months showed a target site late loss index of 11±36% in radiotherapy patients versus 55±30% in controls ($P<0.0001$). A low late loss index was seen in stented and balloon-treated patients and was similar across the 16, 20, and 24 Gy radiotherapy groups. Restenosis (≥50%) rates were significantly lower in radiotherapy patients at the target site (8% versus 39%; $P=0.012$) and at target site plus adjacent segments (22% versus 50%; $P=0.018$). Target lesion revascularization was needed in 5 radiotherapy patients (6%) and 6 controls (24%; $P<0.05$). Stenosis adjacent to the target site and late thrombotic events reduced the overall clinical benefit of radiotherapy.

Conclusions—β-radiotherapy with a centered ^{32}P source is safe and highly effective in inhibiting restenosis at the target site after stent or balloon angioplasty. However, minimizing edge narrowing and late thrombotic events must be accomplished to maximize the clinical benefit of this modality. **(*Circulation*. 2000;102:951-958.)**

Key Words: radiotherapy ■ radiation ■ restenosis ■ radioisotopes ■ stents ■ coronary disease

Radiation therapy with γ- and β-emitting sources inhibits restenosis after percutaneous coronary interventions.[1] Human trials with endovascular γ-radiation demonstrated reduced restenosis in patients with prior restenosis undergoing repeat coronary angioplasty followed by radiotherapy.[2,3] Nonrandomized pilot studies using endovascular β-radiation after balloon angioplasty showed a low late lumen loss and a low restenosis rate in patients with de novo lesions[4] and those with in-stent restenosis.[5]

The Proliferation Reduction with Vascular Energy Trial (PREVENT) is a randomized trial of intracoronary radiation with ^{32}P, a β-emitting source, in patients with restenotic and de novo lesions in whom preradiation treatment with stents or balloon angioplasty was allowed. As such, it represents a trial of β-emitting radiotherapy in a broad spectrum of patients undergoing perculaneous coronary interventions. The primary objective of this study was to demonstrate the safety and performance of intracoronary radiation therapy using an automated source-delivery unit and a source-centering mechanism (Guidant Vascular Intervention). Secondary objectives included evaluating the effectiveness of intravascular radiotherapy after stent implantation compared with balloon angioplasty alone and determining the relative effectiveness of 3 radiotherapy doses (16, 20, and 24 Gy).

Methods

This trial was conducted under a Food and Drug Administration Investigational Device Exemption for a trial of intracoronary radiation therapy. It was approved by the Institutional Review Boards or Ethics Committees and the Radiation Safety Committees of the participating institutions. The study was conducted at the 6 clinical sites listed in the authors' affiliations. The eligibility requirements are shown in Table 1.

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